Coagulopathy and shock on admission is associated with mortality for children with traumatic injuries at combat support hospitals*

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Objective: **In adults, early traumatic coagulopathy and shock are both common and independently associated with mortality. There are little data regarding both the incidence and association of early coagulopathy and shock on outcomes in pediatric patients with traumatic injuries. Our objective was to determine whether coagulopathy and shock on admission are independently associated with mortality in children with traumatic injuries.**

Methods: **A retrospective review of the Joint Theater Trauma Registry from U.S. combat support hospitals in Iraq and Afghanistan from 2002 to 2009 was performed. Coagulopathy was defined as an international normalized ratio of ≥1.5 and shock as a base deficit of ≥6. Laboratory values were measured on admission. Primary outcome was inhospital mortality. Univariate analyses were performed on all admission variables followed by reverse stepwise multivariate logistic regression to determine independent associations.**

Setting: **Combat support hospitals in Iraq and Afghanistan.**

Patients: **Patients <18 yrs of age with Injury Severity Score, international normalized ratio, base deficit, and inhospital mortality were included. Of 1998 in the cohort, 744 (37%) had a complete set of data for analysis.**

Intervention: **None.**

Measurements and Main Results: **The incidence of early coagulopathy and shock were 27% and 38.3% and associated with mortality of 22% and 16.8%, respectively. After multivariate logistic regression, early coagulopathy had an odds ratio of 2.2 (95% confidence interval 1.1– 4.5) and early shock had an odds ratio of 3.0 (95% confidence interval 1.2–7.5) for mortality. Patients with coagulopathy and shock had an odds ratio of 3.8 (95% confidence interval 2.0–7.4) for mortality.**

Conclusions: **In children with traumatic injuries treated at combat support hospitals, coagulopathy and shock on admission are common and independently associated with a high incidence of inhospital mortality. Future studies are needed to determine whether more rapid and accurate methods of measuring coagulopathy and shock as well as if early goal-directed treatment of these states can improve outcomes in children. (Pediatr Crit Care Med 2012; 13:273–277)**

Key Words: base deficit; coagulopathy; combat hospitals; INR; shock; trauma

Trauma remains one of the most common causes of death in all age groups, but this is especially true in the pediatric population. Traumatic injury is the leading cause of death in the United States for patients 1–40 yrs of age (1). Greater than 45% of deaths in children aged 1–14 yrs in the United States are secondary to trauma (1). Up to 47% of these deaths are related to motor vehicle crashes with the rates increasing through adolescence (1). The most common cause of death in pediatric trauma in the United States has been shown to be traumatic brain injury (2). Although the incidence of death from hemorrhage with traumatic injuries has not been described in children, it is the second most common cause of death and the most common cause of medically preventable deaths in adults (3). Children account for 4% to 7% of all admissions to U.S. military hospitals in Afghanistan and Iraq and account for 10% to 12% of all hospital bed days (4, 5). In both combat areas, the most common causes of death are traumatic brain injury (29%) and burns (27%) (6).

The "lethal triad" of trauma emphasizes the relationship among acidosis, hypothermia, and coagulopathy and their association with increased risk of death in adults (3, 7, 8). In adult severe trauma patients, coagulopathy on admission is both common and independently associated with mortality (9). In adult trauma and pediatric burn patients, indicators of shock or acidosis have also been independently associated with increased mortality (10–12). The relationship among acidosis, coagulopathy, severity of injury, and mortality has not been examined simultaneously in a pediatric trauma population. We hypothesize that admission measures of coagulopathy and shock, as measured by the international normalized ratio (INR) and base deficit (BD), will be independently associated with increased mortality in children with traumatic injuries independent of severity of injury.

MATERIALS AND METHODS

A retrospective review of the Joint Theater Trauma Registry from U.S. combat support hospitals in Iraq and Afghanistan from 2002 to 2009 was performed. The Joint Theater

***See also p. 353.**

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Trauma Registry was established by the Department of Defense to collect data on all trauma patients, military and civilian, admitted to combat support hospitals in Iraq and Afghanistan. Patients <18 yrs of age were included in the data collection. Data collected and recorded were admission temperature, heart rate, systolic blood pressure, base deficit, INR, hematocrit, and platelet count. In addition, Injury Severity Score (ISS) 2005, head Abbreviated Injury Score (AIS), Glasgow Coma Score (GCS), injury description, patient sex, and inhospital mortality were recorded. Only those with complete data sets for ISS, BD (mEq/L, INR, AIS, and inhospital mortality were included in the analysis. Admission temperature was not chosen to be one of the mandatory values required to develop our complete data set based on recent data indicating a low incidence of hypothermia in combat casualties and lack of association with mortality (5, 7, 13, 14). Coagulopathy was defined as INR ≥1.5 and shock as BD ≥6. These values are accepted definitions of coagulopathy and shock (7, 13, 15-18). Severe traumatic injury is defined as an ISS of ≥15 and severe traumatic brain injury (TBI) was defined as a head AIS of >2 (19). Head AIS instead of GCS was used to define severe TBI because in this heterogeneous population, GCS could be decreased as a result of causes other than head injury to include hypotension or hypoxemia. Hypothermia was defined as temperature <96°F (20).

The relationships among admission INR (coagulopathy), BD (shock), temperature, GCS, ISS and head AIS, and inhospital mortality were explored. Univariate analyses for mortality were performed on all baseline demographics, vital signs, and laboratory values. Chi-square test was used to compare categorical variables. We measured for collinearity between all variables of interest with the Pearson correlation test with the plan to exclude variables with a high degree of correlation ($r^2 > 0.6$) from our regression analysis. Reverse stepwise multivariate logistic regression was performed with all noncolinear variables that were associated with mortality with a p value of < .2. This was done to adjust for confounding and to determine independent associations with inhospital mortality. Statistical analysis was performed with SPSS (version 15.0; Chicago, IL).

RESULTS

From 2002 to 2009, 1995 patients <18 yrs of age were recorded in the Joint Theater Trauma Registry. From this cohort, 744 (37%) had a complete set of data for this analysis. The median (interquartile range) age was 9 (5–12) years for this cohort and 74.1% (192 of 744) were male. Cause of injury is described in Figure 1. Overall mortality for this cohort was 8.7% (65 of 744), almost identical to the excluded cohort. Complete demographics and comparisons between patients analyzed and those excluded as a result of incomplete data sets are noted in Table 1. Although there are statistical differences in patient age, ISS, and admission arterial saturation of peripheral oxygen, none appear to be clinically significant between patients included or excluded from our analysis. However, there is a significantly increased incidence of severe TBI in the patients included vs. excluded from analysis (Table 1). The following variables were determined to be associated with mortality: age, heart rate, systolic blood pressure, GCS, hematocrit, base deficit, INR, head AIS (severe TBI), and ISS. Table 3 indicates that of these variables, only INR, BD, GCS, and ISS were independently associated with mortality according to the logistic regression analysis performed.

Hypothermia on admission was not associated with mortality. The incidence of hypothermia was 2.8% (15 of 542) in survivors and 5.4% (two of 17) in nonsurvivors (p = .28). GCS and ISS were both associated with mortality (p < .001). For survivors, median GCS was 15 (13–15) and ISS was 10 (5–18), whereas for nonsurvivors, median GCS was 3 (3–11) and ISS was 25 (15–29). The mortality rate was 18% (37 of 205) for those with

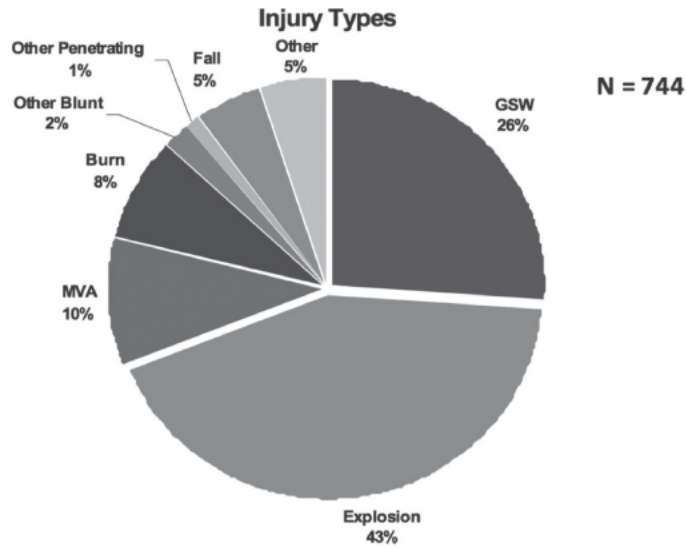

Figure 1. Distribution of mechanisms of injury. *GSW*, gunshot wound; *MVA*, motor vehicle accident.

Table 1. Comparison between selected cohort and those with incomplete data sets

	Included No.	Included Cohort	Excluded No.	Excluded Cohort	p
Age, yrs	744	9 (5–12)	1251	8 (4–12)	<.001
Male sex, %	743	74.1 (551/744)	1251	73.5 (920/1251)	.86
Injury Severity Score	744	10 (5–19)	1251	9 (4–16)	<.001
Temperature, °F	611	98.9 (97.8–99.7)	929	98.7 (97.8–99.8)	.94
Heart rate, beats/min	727	120 (103–141)	1117	121 (101–144)	.38
Respiration rate, breaths/min	504	24 (20–30)	861	24 (20–30)	.83
Arterial saturation of peripheral oxygen	684	100 (98–100)	413	99 (98–100)	<.01
Systolic blood pressure, mm Hg	714	117 (104–129)	1037	118 (105–129)	.39
Hematocrit, %	722	34 (29.4–38.0)	276	33.2 (28.0–37.5)	.35
Platelet count	707	325 (248–414)	254	336 (246–442)	.26
International normalized ratio	744	1.2 (0.9–1.5)	84	1.1 (0.9–1.4)	.29
Coagulopathy	744	27.2 (202/744)	84	21.4 (18/66)	.30
Base deficit, mEq/L	744	4 (2–7)	141	5 (2–8)	.23
Shock	744	38.3 (285/744)	141	40.4 (57/141)	.64
Head Abbreviated Injury Score ≥3, %	744	27.6 (205/744)	1251	17.3 (217/1251)	<.01
Glasgow Coma Score	707	15 (10–15)	829	15 (13–15)	.09
Ventilator days	734	0 (0–2)	1156	0 (0–1)	.28
Hospital days	737	3 (1–7)	1181	3 (1–8)	.7
Inhospital mortality, %	744	8.7 (65/744)	1251	8.6 (107/1251)	.93

Data presented as median (interquartile range).

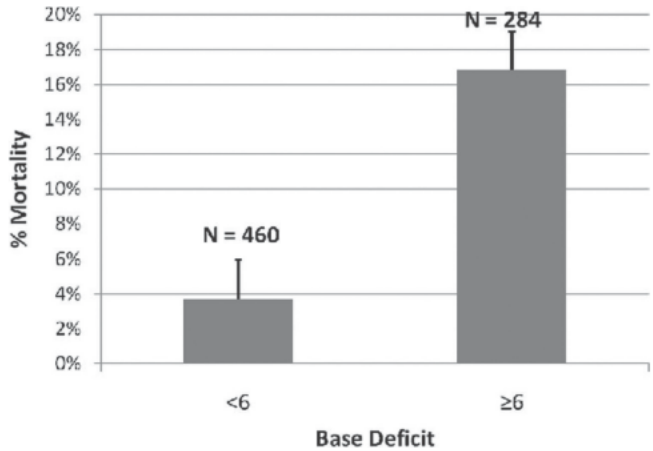

Figure 2. Mortality according to admission international normalized ratio. Error bars represent 95% confidence interval.

Table 3. Mortality according to Injury Severity Score and the presence of coagulopathy or shock

	Injury Severity Score 0–14		Injury Severity Score ≥15	
	Noncoagulopathic	Coagulopathic[a]	Noncoagulopathic	Coagulopathic[a]
Coagulopathy	80% (361/452)	20% (91/452)	62% (181/292)	38% (111/292)[b]
Mortality	1.1% (4/361)	13% (12/91)[a]	9.4% (17/181)	29% (32/111)[a]
	No Shock	Shock	No Shock	Shock
Shock	67% (302/452)	33% (150/452)[a]	54% (157/292)	46% (135/292)[a,b]
Mortality	1.0% (3/302)	9.3% (14/150)[a]	8.9% (14/157)	26% (35/135)*a*

[a]$p < .01$ for all values when compared with the corresponding noncoagulopathic group; [b]$p < .01$ compared with Injury Severity Score 0–14 coagulopathic group.

Table 2. Logistic regression results for inhospital mortality

Variable	Odds Ratio (95% confidence interval)	*p*
Injury Severity Score	1.1 (1.1–1.1)	<.001
Coagulopathy	2.2 (1.1–4.5)	.025
Shock	3.0 (1.1–7.5)	.019
Glasgow Coma Score	0.85 (0.80–0.91)	<.001

severe TBI vs. 5.2% (28 of 539) for those without severe TBI ($p < .001$). Collinearity was not identified among any of the variables listed in Table 1.

Coagulopathy. On admission, 27% (202 of 744) of patients presented with early coagulopathy. The mortality rate was 22% (44 of 202) for coagulopathic patients compared with a mortality rate of 3.9% (21 of 542) for patients without early coagulopathy ($p < .001$) (Fig. 2). This relationship was also independent of injury severity measured by ISS score (Table 2). By logistic regression, the odds ratio (OR) of mortality with early coagulopathy is 2.2 (95% confidence interval [CI] 1.1– 4.5) ($p = .025$). INR is also independently associated with mortality as a continuous variable with an OR of 2.1 (95% CI 1.4–3.3).

Shock. On admission, 38.3% (285 of 744) of the patients presented with early shock with a mortality rate of 16.8% (48 of 285) compared with a mortality rate of 3.7% (17 of 459) in those without shock ($p < .001$) (Fig. 3). This relationship was also independent of injury severity measured by ISS score (Table 2). On multivariate statistical analysis, the OR for mortality with early shock (BD ≥6) was 3.0 (95% CI 1.2–7.5) ($p = .019$). When early coagulopathy and shock were both present, the OR was 3.8 (95% CI 2.0–7.4) for mortality ($p < .001$). BD, as a continuous variable, is independently associated with death with an OR of 1.12 (95% CI 1.05–1.20).

Of those patients presenting in shock, 40% (114 of 285) were coagulopathic. For patients presenting with early coagulopathy, 56% (114 of 202) were in shock. The Pearson's correlation r^2 value was 0.40 ($p < .01$) between BD and INR measured continuously.

DISCUSSION

Our objective in this study was to evaluate if early coagulopathy (admission INR ≥1.5) and shock (admission BD ≥6) were independently associated with inhospital mortality in children with traumatic injuries treated at combat support hospitals in Iraq and Afghanistan. Our article is unique in that we have analyzed many potential variables for their relationship with mortality, including admission INR, BD, GCS, temperature, hematocrit, age, systolic blood pressure, ISS, and head AIS. A few previous pediatric studies have documented an independent association between shock on admission and increased mortality, but they did not simultaneously evaluate measures of coagulopathy, BD, ISS, GCS, and head AIS as covariates (11, 12, 21). Our results indicate an independent association between coagulopathy and shock with increased mortality for patients with and without severe injury (7, 9). This is important because it infers that severe anatomic injury is not required for patients to be at increased risk of mortality from early coagulopathy and or shock (as noted in the mortality difference within the ISS 0–14 group, Table 2). It also suggests that it may be beneficial to screen for these conditions and treat them early in patients without severe injury to potentially improve outcomes by decreasing death from coagulopathy or shock if present.

Our results also indicate that lower admission GCS was independently associated with mortality and increased head AIS values were not. Despite the lack of collinearity, it is possible that the simultaneous evaluation of head AIS and GCS affected the logistic regression analysis. Alternatively, a functional measure of central nervous system injury (GCS) may be a more accurate predictor of mortality than an anatomical measure of injury (head AIS). Both of these measures have been shown to predict mortality, although similar to our findings, other authors have also seen no correlation between these two markers (22).

As hypothesized, our results were similar to those previously reported for adults with severe traumatic injuries (7, 9, 23). In our analysis, 27% of the children admitted to combat support hospitals were coagulopathic. Also consistent with adult reports, children with early

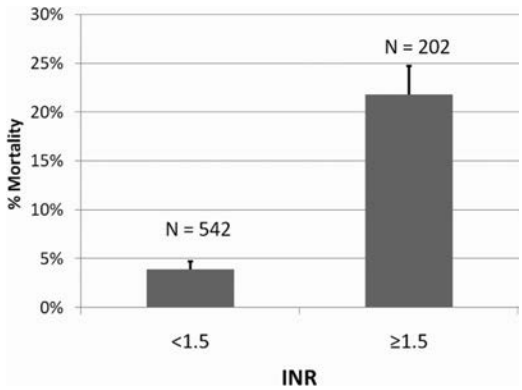

Figure 3. Mortality according to admission base deficit (mEq/L). Error bars represent 95% confidence interval. *INR*, international normalized ratio.

coagulopathy or shock were found to have significantly worse inhospital mortality independent of injury severity. In children with more severe injuries as measured by ISS, there was an increased incidence of coagulopathy and shock with corresponding increased mortality as can be noted on Table 2 (7, 9).

Recently, mechanisms have been described that indicate early hypoperfusion or shock leads to coagulopathy through activated protein C and other anticoagulant pathways (24). In general, these reviews indicate that local hypoperfusion is associated with increased endothelial injury, leading to increased activated protein C and tissue plasminogen activator concentrations on admission in patients with severe traumatic injury (24, 25). There is also evidence that this early trauma-induced coagulopathy is associated with decreased tissue factor pathway inhibitor and tissue activated fibrinolysis inhibitor concentrations (24, 25). Therefore, there appears to be a link between early shock and coagulopathy that provides biologic plausibility for our results. This relationship between admission shock and coagulopathy has been previously reported in adults, and is just one of many potential causes for coagulopathy in trauma patients (24, 25). The realization that there are many factors that contribute to coagulopathy is a plausible explanation for why there is a weak correlation between INR and BD in our cohort and that not all patients with shock also present with coagulopathy and that not all coagulopathic patients are in shock.

Our analysis identifies reversible factors that, if recognized and treated early and aggressively, may improve outcomes in children with severe traumatic injuries. Spinella and Holcomb (3) have recently reviewed the controversial concept of damage control resuscitation, which includes the early and increased use of plasma and platelets and the avoidance of older red blood cells for patients with massive bleeding. This approach is intended to correct early coagulopathy and shock and has been independently associated with improved survival and decreased death from hemorrhage in multiple retrospective studies (3, 26). In addition, studies by Nunez and Cotton have both documented that the use of massive transfusion protocols that use damage control resuscitation strategies were associated with improved outcomes in patients who have coagulopathy and shock addressed early (23). Pediatric massive transfusion protocols have also been recently described that use the concepts of damage control resuscitation (3). Recent evidence indicates that the transfusion of fresh compared with older red blood cells improves oxygen delivery, reverses shock, and is independently associated with decreased mortality and death from multiorgan failure (27–33). Two large pediatric retrospective studies also indicate decreased new or progressive organ failure was associated with the transfusion of fresh red blood cells (34, 35). Prospective studies are being performed or are in development to determine whether the reversal of shock with red blood cells of decreased storage duration improves outcomes in both critically ill children and adults (36).

There are several limitations to our study. First, penetrating injuries were more common in this cohort than blunt injuries, which may limit its generalizability, because the injuries associated with pediatric trauma in the United States are predominantly blunt in nature (1). In addition, the Joint Theater Trauma Registry does not take into account the prehospital transport time, which could potentially alter the patient's physiological state on admission. We also were not able to identify which patients were part of mass casualty events. The retrospective nature of this analysis may have also introduced selection bias. Those who did not have admission BD and INR values sampled could be dissimilar regarding severity of injury and risk of early coagulopathy or shock. Although the patients included in the analysis had increased age, increased ISS, and increased arterial saturation of peripheral oxygen, there were no significant differences in INR, BD, or mortality measured when compared with patients not included. There was an increased incidence of severe TBI, according to head AIS, noted in the cohort that was used. This indicates some selection bias in our model. Because the variables measured in the Joint Theater Trauma Registry were limited, there is still a potential for additional selection bias, which may have affected the accuracy of our multivariate logistic regression analysis. In particular, temperature was recorded for 77% (577 of 744) of the patients analyzed and there was a nonsignificant trend for increased hypothermia in nonsurvivors. However, the overall incidence of hypothermia was relatively low (2.9%), and there were only two nonsurvivors in our database that had documented hypothermia. We appropriately chose to not include admission temperature as a mandatory variable for patient inclusion in this study based on recent analyses (post-2005) indicating that admission temperature was not associated with mortality in casualties treated at combat support hospitals (5, 7, 13, 14). Our results that admission hypothermia was not associated with mortality are likely a result of the low frequency of hypothermia in our cohort rather than the lack of a relationship between hypothermia on admission and risk of mortality in children. Finally, we recognize that our definition of shock according to a BD value of ≥ 6 is arbitrary. This threshold has been used previously and is more conservative than other definitions (10-13, 37).

Future research is needed to determine whether early detection and correction of coagulopathy and shock can improve outcomes and if so, which interventions can optimally reverse these conditions. In addition, prehospital methods that might reduce the risk of developing early coagulopathy and shock also require study. Unfortunately, the standard trauma databases used by all Level I-verified American College of Surgeons pediatric trauma centers do not require the collection of measures of

shock and coagulopathy nor does it require transfusion data. This must change if we are going to perform more robust outcomes analyses for children with traumatic injuries. Finally, predictive tools that incorporate both physiological variables and anatomic severity of injury scores need to be developed in children with traumatic injuries to improve their accuracy because it appears that measures of coagulopathy and shock are associated with mortality. A scoring system to classify specifically which pediatric patients are at highest risk for mortality may have clinical use and be valuable for research and quality assurance projects.

CONCLUSIONS

In this study, we have demonstrated the association of early coagulopathy and shock with mortality in a pediatric trauma population. Future studies are needed to assess whether early, goal-directed treatment can improve outcomes in these patients.

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